GELFOAM® absorbable gelatin powder
(Absorbable gelatin powder from absorbable gelatin sponge, USP)

DESCRIPTION

GELFOAM is a medical device intended for application to bleeding surfaces as a hemostatic. It is a water-insoluble, off-white, nonelastic, porous, pliable product prepared from purified pork Skin Gelatin USP Granules and Water for Injection, USP. It is able to absorb and hold within its interstices, many times its weight of blood and other fluids. GELFOAM® Sterile Powder is a fine, dry, heat-sterilized light powder prepared by milling absorbable gelatin sponge.

ACTION

GELFOAM has hemostatic properties. While its mode of action is not fully understood, its effect appears to be more physical than the result of altering the blood clotting mechanism. When not used in excessive amounts, GELFOAM is absorbed completely, with little tissue reaction. This absorption is dependent on several factors, including the amount used, degree of saturation with blood or other fluids, and the site of use. When placed in soft tissues, GELFOAM is usually absorbed completely in from four to six weeks, without inducing excessive scar tissue. When applied to bleeding nasal, rectal or vaginal mucosa, it liquefies within two to five days.

INDICATIONS

Hemostasis: GELFOAM® Sterile Powder, saturated with sterile sodium chloride solution, is indicated in surgical procedures, including those involving cancellous bone bleeding, as a hemostatic device, when control of capillary, venous, and arteriolar bleeding by pressure, ligature, and other conventional procedures is either ineffective or impractical.

DIRECTIONS FOR USE

GELFOAM® Sterile Powder can be saturated with sterile isotonic sodium chloride solution (sterile saline), before use as an adjunct to hemostasis. The jar of GELFOAM® Sterile Powder should be opened and the contents (1 gram) poured carefully into a sterile beaker, avoiding contamination. Using sterile techniques, a putty-like paste is prepared by adding a total of approximately 3-4 mL of sterile saline to the GELFOAM. Dispersion of the powder can be avoided by initially compressing it with the gloved fingers into the bottom of the beaker and then kneading it into the desired consistency. The resulting doughy paste may be smeared or pressed against the bleeding surface to control bleeding. When bleeding stops the excess should be removed. Use only the minimum amount of GELFOAM, necessary to produce hemostasis. When necessary, GELFOAM may be left in place at the bleeding site. Since GELFOAM causes little more cellular reaction than does

the blood clot, the wound may be closed over it. GELFOAM may be left in place when applied to mucosal surfaces until it liquefies.

CONTRAINDICATIONS

- GELFOAM should not be used in the closure of skin incisions because it may interfere with healing of the skin edges. This is due to mechanical interposition of gelatin and is not secondary to intrinsic interference with wound healing.

- Do not use GELFOAM in intravascular compartments, because of the risk of embolization.

- Do not use GELFOAM sterile powder in patients with known allergies to porcine collagen.

WARNINGS

- GELFOAM is not intended as a substitute for meticulous surgical technique and the proper application of ligatures, or other conventional procedures for hemostasis.

- GELFOAM is supplied as a sterile product and cannot be resterilized. Unused, opened jars of GELFOAM should be discarded.

- Only the minimum amount of GELFOAM necessary to achieve hemostasis should be used. Once hemostasis is attained, excess GELFOAM should be carefully removed.

- The use of GELFOAM is not recommended in the presence of infection. GELFOAM should be used with caution in contaminated areas of the body. If signs of infection or abscess develop where GELFOAM has been positioned, reoperation may be necessary in order to remove the infected material and allow drainage.

- The safety and efficacy of the combined use of GELFOAM with other agents such as topical thrombin has not been evaluated in controlled clinical trials and therefore cannot be recommended. If in the physician's judgment, concurrent use of topical thrombin or other agents are medically advisable, the product literature for that agent should be consulted for complete prescribing information.

- While packing a cavity for hemostasis is sometimes surgically indicated, GELFOAM should not be used in this manner unless excess product not needed to maintain hemostasis is removed.

- Whenever possible, GELFOAM should be removed after use in laminectomy procedures and from foramina in bone, once hemostasis is achieved. This is because GELFOAM may swell after absorbing fluids, and produce nerve damage

by pressure within confined bony spaces. The packing of GELFOAM, particularly within bony cavities, should be avoided, since swelling may interfere with normal function and/or possibly result in compression necrosis of surrounding tissues.

PRECAUTIONS

The minimum amount of GELFOAM® Sterile Powder needed for hemostasis should be applied together with pressure until the bleeding stops. The excess should then be removed. GELFOAM should not be used for controlling postpartum hemorrhage or menorrhagia. It has been demonstrated that fragments of another hemostatic agent, microfibrillar collagen, pass through the 40 micron transfusion filters of blood scavenging systems. GELFOAM should not be used in conjunction with autologous blood salvage circuits since the safety of this use has not been evaluated in controlled clinical trials. Microfibrillar collagen has been reported to reduce the strength of methyl-methacrylate adhesives used to attach prosthetic devices to bone surfaces. As a precaution, GELFOAM should not be used in conjunction with such adhesives. GELFOAM is not recommended for the primary treatment of coagulation disorders. It is not recommended that GELFOAM be saturated with an antibiotic solution or dusted with antibiotic powder.

ADVERSE REACTIONS

There have been reports of fever associated with the use of GELFOAM, without demonstrable infection. GELFOAM may serve as a nidus for infection and abscess formation[1], and has been reported to potentiate bacterial growth. Giant-cell granuloma has been reported at the implantation site of absorbable gelatin product in the brain[2], as has compression of the brain and spinal cord resulting from the accumulation of sterile fluid.[3] Foreign body reactions, "encapsulation" of fluid and hematoma have also been reported. When GELFOAM was used in laminectomy operations, multiple neurologic events were reported, including but not limited to cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence. Excessive fibrosis and prolonged fixation of a tendon have been reported when absorbable gelatin products were used in severed tendon repair. Toxic shock syndrome has been reported in association with the use of GELFOAM in nasal surgery. Fever, failure of absorption, and hearing loss have been reported in association with the use of GELFOAM during tympanoplasty.

ADVERSE REACTIONS REPORTED FROM UNAPPROVED USES

GELFOAM is not recommended for use other than as an adjunct for hemostasis. While some adverse medical events following the unapproved use of GELFOAM have been reported to Pharmacia & Upjohn Company (see ADVERSE REACTIONS), other hazards associated with such use may not have been reported. When GELFOAM has been used during intravascular catheterization for the purpose of producing vessel occlusion, the following adverse events have been reported; fever, duodenal and pancreatic infarct, embolization of lower extremity vessels,

pulmonary embolization, splenic abscess, necrosis of specific anatomic areas, asterixis, and death. These adverse medical events have been associated with the use of GELFOAM for repair of dural defects encountered during laminectomy and craniotomy operations: fever, infection, leg paresthesias, neck and back pain, bladder and bowel incontinence, cauda equina syndrome, neurogenic bladder, impotence, and paresis.

ADVERSE EVENTS ASSOCIATED WITH BONE HEMOSTASIS

In a clinical study, 108 patients received GELFOAM® Sterile Powder on the cut surface of the sternum during cardiopulmonary bypass surgery, while 107 patients received no treatment on the cut surface of the bone. Table 1 is a summary of medical events reported by at least 1.0% of patients a treatment group. The most frequently reported events were atrial fibrillation, perioperative event, and wound infection. Events occurring in less than 1.0% of the patients were as follows: anaphylaxis, cardiogenic shock, delirium tremens, infection at the vascular catheter site, unevaluable reaction, sepsis, angina pectoris, atrial arrhythmia, nodal arrhythmia, arteriosclerosis, cardiac insufficiency, cardiac tamponade, cardiomyopathy, deep vein thrombosis, mitral valve disorder, endocarditis, ventricular extrasystoles, heart arrest, hypotension, mesenteric occlusion, superventricular tachycardia, thrombophlebitis, thrombosis, gastrointestinal disorder, gastrointestinal bleeding, increased serum creatinine, dehydration, anemia, thrombocytopenia, abnormal healing, hypovolemia, hypoxia, metabolic acidosis, cerebral infarction, visual hallucinations, stupor, aspiration pneumonia, chest congestion, pleural effusion, pulmonary infiltration, retinal artery occlusion, anuria, UG disorder, abnormal kidney function and menorrhagia.

Table 1: Summary of Medical Events for Gelfoam Sterile Powder when used as a Bone Hemostatic Agent During Cardiopulmonary Bypass Surgery.

Medical Event	GELFOAM N=108		Control N=107		Total N=215	
	n	%	n	%	n	%
Atrial Fibrillation	14	(13.0)	12	(11.2)	26	(12.1)
Wound Infection	6	(5.6)	1	(0.9)	7	(3.3)
Perioperative Event	4	(3.7)	5	(4.7)	9	(4.2)
Congestive Heart Failure	4	(3.7)	0	(0.0)	4	(1.9)
Ventricular Tachycardia	2	(1.9)	3	(2.8)	5	(2.3)
Atrial Flutter	2	(1.9)	0	(0.0)	2	(0.9)
Peripheral Vascular Disorder	2	(1.9)	0	(0.0)	2	(0.9)
Pneumothorax	2	(1.9)	3	(2.8)	5	(2.3)
Respiratory Failure	2	(1.9)	2	(1.9)	4	(1.9)
Respiratory Arrest	2	(1.9)	1	(0.9)	3	(1.4)
Fever	1	(0.9)	2	(1.9)	3	(1.4)
Heart Block	1	(0.9)	2	(1.9)	3	(1.4)
Prolonged Wound Drainage	0	(0.0)	1	(0.9)	1	(0.5)
Cellulitis	0	(0.0)	2	(1.9)	2	(0.9)
Dyspnea	0	(0.0)	2	(1.9)	2	(0.9)
Pneumonia	0	(0.0)	2	(1.9)	2	(0.9)

In general, the following adverse events have been reported with the use of absorbable porcine gelatin-based hemostatic agents:

- Gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation and have been reported to potentiate bacterial growth.
- Giant cell granulomas have been observed at implant sites when used in the brain.
- Compression of the brain and spinal cord resulting from the accumulation of sterile fluid has been observed.
- Multiple neurologic events were reported when absorbable gelatin-based hemostatic agents were used in laminectomy operations, including cauda equina syndrome, spinal stenosis, meningitis, arachnoiditis, headaches, paresthesias, pain, bladder and bowel dysfunction, and impotence and paresis.
- The use of absorbable gelatin-based hemostatic agents have been associated with paralysis, due to device migration into foramina in the bone around the spinal cord, and blindness due to device migration in the orbit of the eye, during lobectomy, laminectomy and repair of a frontal skull fracture and lacerated lobe.

- Foreign body reactions, "encapsulation" of fluid, and hemotoma have been observed at implant sites.

- Excessive fibrosis and prolonged fixation of a tendon have been reported when absorbable gelatin-based sponges were used in severed tendon repair.

- Toxic shock syndrome was reported in association with the use of absorbable gelatin-based hemostats in nasal surgery.

- Fever, failure of absorption, and hearing loss have been observed when absorbable hemostatic agents were used during tympanoplasty.

CLINICAL STUDIES

GELFOAM Sterile Sponge is a water-insoluble, hemostatic device prepared from purified skin gelatin, and capable of absorbing up to 45 times its weight of whole blood.[4] The absorptive capacity of GELFOAM is a function of its physical size, increasing as the size of the gelatin sponge increases.[5] The mechanism of action of surface-mediated hemostatic devices is supportive and mechanical.[5] Surface acting devices, when applied directly to bleeding surfaces, arrest bleeding by the formation of an artificial clot and by producing a mechanical matrix that facilitates clotting.[6] Jenkins et al [7] have theorized that the clotting effect of GELFOAM may be due to release of thromboplastin from platelets, occurring when platelets entering the sponge become damaged by contact with the walls of its myriad of interstices. Thromboplastin interacts with prothrombin and calcium to produce thrombin, and this sequence of events initiates the clotting reaction. The authors suggest that the physiologic formation of thrombin in the sponge is sufficient to produce formation of a clot, by its action on the fibrinogen in blood.[7] The spongy physical properties of the gelatin sponge hasten clot formation and provide structural support for the forming clot.[6,8] Several investigators have claimed that GELFOAM becomes liquefied within a week or less and is completely absorbed in four to six weeks, without inducing excessive scar formation.[4,7,9,10,11] Barnes[10] reviewed experiences with GELFOAM in gynecologic surgery. No excessive scar tissue, attributable to the absorption of GELFOAM, could be palpated at postoperative examination.

Bone Hemostasis Study:

The efficacy of GELFOAM® Sterile Powder as a bone hemostatic agent during cardiopulmonary bypass surgery was evaluated

Study Design

Two randomized open-label clinical studies were conducted at separate investigative sites. The objectives were as follows:

- To evaluate the effectiveness of GELFOAM Sterile Powder as a hemostatic agent in the treatment of sternal bone bleeding during cardiopulmonary bypass surgery.

- To identify any deleterious effects of GELFOAM™ Sterile Powder on interference with bone healing.

- To determine any systemic or local wound side effects from leaving GELFOAM™ Sterile Powder *in situ*.

Patients between the ages of 18 to 74 years old undergoing cardiopulmonary bypass surgery were randomly assigned to either a GELFOAM group or a Control group. The GELFOAM group (composed of 108 patients) had a paste made up of Sterile saline solution and GELFOAM sterile powder applied to the cut sternal surface immediately following sternotomy. The Control group (composed of 107 patients) received no treatment applied to the cut surface.

Blood loss was monitored both during surgery and postoperatively. Blood loss during surgery was determined by measuring the weight of the powder before and after application to the cut edge of the sternum. Postoperative blood loss was collected from the mediastinal drainage tubes. The total blood loss (in milligrams) over 72 hours was determined for each patient.

Study Endpoints

Patients were evaluated upon admission (preoperative), during surgery (intraoperative), after surgery (postoperative), upon hospital discharge (7 to 10 days after surgery), and at the 3-month follow-up visit. An additional post study follow-up was required if a patient reported an ongoing medical event at the 3-month follow-up visit.

Study Results

In both studies, the amount of blood loss was significantly less in the GELFOAM group than in the control group. In Study 001, the mean blood loss in the GELFOAM group was 13727.7 mg while the mean blood loss in the Control group was more than double at 27712.0 mg. Similar results were found in Study 002, where the mean blood loss in the GELFOAM group was 9514.8 mg while the mean blood loss in the Control group was 22687.5 mg.

Table 2: Blood Loss in Sternotomy Patients				
	Site 001		Site 002	
	GELFOAM	Control	GELFOAM	Control
Mean Blood Loss (mg)	13727.7	27712.0	9514.8	22687.5
Median Blood Loss (mg)	11561.0	24798.0	6950.0	16900.0
Minimum Blood Loss (mg)	2922.0	10748.0	800.0	900.0
Maximum Blood Loss (mg)	87448.0	61535.0	46000.0	89800.0

Patients in the GELFOAM and Control groups were similar with regard to sternal bone healing. At hospital discharge, normal bone healing was reported for 105 patients (97%) in the GELFOAM group and 104 patients (97%) in the Control group. At the 3-month follow-up, 103 patients (95%) in the GELFOAM group and 100 patients (93%) in the Control group were healed.

Few patients in either treatment group had sternotomy infection or other postoperative infection complications related to sternotomy. At hospital discharge, two GELFOAM-treated patients had mediastinitis. No Control patients had any infections at hospital discharge. One GELFOAM-treated patient had a non-infection-related complication.

At the 3-month follow-up, one of the original GELFOAM patients who had mediastinitis still showed signs of infection. In addition, two additional GELFOAM-treated patients developed mediastinitis at the 3-month follow up.

One patient in the CONTROL group experienced sternal osteomyelitis at the 3-month follow-up but recovered with no residual effects. No patients from the GELFOAM arm of the study had reported complications of sternal osteomyelitis.

There was a total of four CONTROL patients who had non-infection related complications. One CONTROL patient had serous/sanguineous wound drainage from the left leg and sternum incisions at hospital discharge. This complication was non-infectious and the patient recovered with no residual side effects.

Three CONTROL patients all experienced chronic pain syndrome, a symptom which can occur following thorasic/cardiac surgery. Evaluation sternal bone healing at the 3-month follow-up for these patients showed no evidence of non-union of the sternum. In all three cases, bone healing at the 3-month follow-up was reported as being normal. A summary of sternotomy infection information is located in Table 3.

Table 3 SUMMARY OF POSTEROPERATIVE INFECTION COMPLICATIONS

	HOSPITAL DISCHARGE				3-MONTH FOLLOW-UP			
	GELFOAM		Control		GELFOAM		Control	
	N	%	N	%	N	%	N	%
Any Infection								
yes	1	(1)	0	(0)	5	(5)	0	(0)
no	104	(99)	106	(100)	95	(95)	105	(100)
Superficial Wound								
yes	0	(0)	0	(0)	2	(2)	0	(0)
no	105	(100)	106	(100)	98	(98)	105	(100)
Sternal Osteomyelitis								
yes	0	(0)	0	(0)	1	(1)	1	(1)
no	105	(100)	106	(100)	99	(99)	105	(99)
Mediastinitis								
yes	1	(1)	0	(0)	2	(2)	0	(0)
no	104	(99)	106	(100)	98	(98)	105	(100)
Complication Related to Sternotomy								
Yes	0	(0)	0	(0)	1	(1)	3	(3)
No	105	(100)	106	(100)	99	(99)	102	(97)

Study Conclusions

These studies demonstrate that a paste made from GELFOAM® Sterile Powder is safe and effective in treating intraoperative bleeding when applied to the cut surface of cancellous bone and has shown superior hemostasis versus no treatment at all to the cut bone surface. The benefit to patients is that a reduction in bleeding will make surgery easier to perform by reducing the time the surgeon needs to revisit cut bone surfaces to clean up the bleeding. This study also demonstrated that GELFOAM® Sterile Powder could be left *in situ* without increased risk of bone infection or nonunion of the sternum.

DOSAGE AND ADMINISTRATION

Sterile technique should always be used. The minimum amount of GELFOAM should be applied to the bleeding site (see DIRECTIONS FOR USE) with pressure until hemostasis is observed. Opened jars of unused GELFOAM should always be discarded.

HOW SUPPLIED

GELFOAM® Sterile Powder (absorbable gelatin powder) is supplied in jars containing 1 gram, NDC 0009-0433-01.

STORAGE AND HANDLING

GELFOAM Sterile Powder should be stored at controlled room temperature 20° to 25°C (68° to 77°F) [see USP]. Once the jar is opened, contents are subject to contamination. It is recommended that GELFOAM be used as soon as the jar is opened and unused contents discarded.

Caution: Federal law restricts this device to sale by or on the order of a physician.

ANIMAL PHARMACOLOGY

Surface acting hemostatic devices, when applied directly to bleeding surfaces, arrest bleeding by providing a mechanical matrix that facilitates clotting.[6, 8,13,14] Due to their bulk, surface-acting hemostatic agents slow the flow of blood, protect the forming clot, and offer a framework for deposition of the cellular elements of blood.[6, 7,8,13] MacDonald and Mathews [12] studied GELFOAM implants in canine kidneys and reported that it assisted in healing, with no marked inflammatory or foreign-body reactions. Jenkins and Janda[13] studied the use of GELFOAM in canine liver resections and noted that the gelatin sponge appeared to offer a protective cover and provide structural support for the reparative process. Correll et al[14] studied the histology of GELFOAM Sterile Sponge when implanted in rat muscle and reported no significant tissue reaction.

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